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IN THE UNITED STATES PATENT OFFICE

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Title: TREATMENT OF DISEASE EMPLOYING HYALURONIC ACID AND NSAIDS

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Examiner: DR. KATHLEEN FONDA

Group Art Unit: 1211 Due Date: July 16, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF GEORGE A. DEVEBER
under §1.132

I, GEORGE A. DEVEBER, make oath and say as follows:

1. I am a Medical Doctor qualified in general internal medicine (FRCP) (C) and a practicing nephrologist for in excess of 30 years now, certified by the American Board

of Internal Medicine. I obtained my medical undergraduate degree from the University of Toronto.

2. Now shown to me and marked as **Exhibits A and B** to this my Declaration is a copy of my Curriculum Vitae and Bibliography respectively.

3. I am a Medical Consultant to the Assignee, Hyal Pharmaceutical Corporation, of U.S. Patent Application Serial No. 07/675,908 which is, I am advised by Ivor Hughes, Counsel to Hyal Pharmaceutical Corporation, the National Entry Application into the United States from PCT International Publication No. WO 91/04058 filed September 18, 1990.

4. As a Medical Consultant, I was involved in advising Hyal Pharmaceutical Corporation and have carried out research and development and ~~testing~~ broader for Hyal Pharmaceutical Corporation. I would not, however, let my acting as a Consultant for Hyal Pharmaceutical Corporation or for anyone, interfere with or cloud my professional objectivity and responsibilities in preparing any declaration.

5. I consider myself to have in-depth knowledge of the products of Hyal and their use and application. These products include forms of hyaluronic acid for example, sodium hyaluronate having various molecular weights, amounts and percentage concentrations. I have, as well, written confidential articles with respect to the medical applications and uses of hyaluronic acid. These articles are kept on file at Hyal Pharmaceutical Corporation's offices.

6. I have read the application 07/838,675 and as a medical doctor I would have no troubles from the teachings of this application determining the appropriate

dosage amounts given the fact that I know from the examples that the formulations containing between 1% and 3% hyaluronic and 1% and 5% NSAID are effective to treat and resolve basal cell carcinoma and the fact that accumulation of the composition in the epidermis of the skin is taught in the application. This accumulation is shown in the tests at pages 28-33 and pages 49-51 of the application. The blood levels test at pages 49-51 shows that the formulation does not enter the blood and thus would be accumulated in the skin and discharged through the lymphatic system. It would be easy for me to conduct tests on a limited number of individuals having basal cell carcinoma or arrange for tests to be conducted on individuals having basal cell carcinoma using various amounts of the formulations taught in the application to determine optimal dosage amounts. These tests would require minimum effort and not constitute experimentation as I am already aware that the administration of the formulations resolves the basal cell carcinoma. The application specifies several dosages (for example, 20 mg/cm^2 of the form of hyaluronic acid and 2 grams of the formulation). I would start with these formulations in my tests to determine optimal dosages that I would prescribe.

7. I would also have no trouble specifying the period of time and number of applications daily for the use of such formulation. Persons skilled in the art would understand these expressions. The phrases are ordinary English and such persons would know to prescribe the use of the formulations a number of times daily over a period of time sufficient to clear and resolve the basal cell carcinoma. The patent application specifically teaches through its examples that the basal cell carcinoma is cleared using the formulations. Persons skilled in the art would have no difficulty understanding these expressions with respect to the method of treatment. Finally, with respect to the expression "molecular weight", persons skilled in the art would have no trouble understanding the expression "molecular weight" and what is

suitable to be used. The molecular weights of the amounts of hyaluronan used also refer to the supplier who can be easily contacted for information if required. No misunderstanding is created by the expression "molecular weight".

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 10th day of October, 1996.

GEORGE A. DEVEBER MD FACOG

AH. #39

EXHIBIT A

GEORGE A. DEVEBER, M.D., F.R.C.P.(C)

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Toronto, Ontario
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CURRICULUM VITAE

SUMMARY

1. Experienced physician with extensive background in hospital, corporate and academic fields, including managerial and executive roles. Has developed key networking contacts throughout the healthcare, government, biotechnology and academic communities. Skilled in project management, staff recruitment and development. Current activities include Medical Director of Hyal Pharmaceutical Corporation, Vasogen Inc. and provision of consulting services to Baxter Corporation and Hyal Pharmaceutical Corporation.

EXPERIENCE - ACHIEVEMENTS

2. HYAL PHARMACEUTICAL CORPORATION — Jan. 1, 1994-present
Medical Director

(a) Responsibility in respect of clinical trials with respect to formulations using hyaluronic acid (sodium hyaluronate) alone or in conjunction with medicines for example the NSAID diclofenac;

(b) Wrote internal corporate review of Biology, Pharmacology clinical trials and potential applications of compositions containing hyaluronic acid (sodium hyaluronate).

3. VASOGEN INC.
Medical Director — 1994-present

(a) Responsible for clinical development, clinical trials and regulatory affairs.

4. BAXTER CORPORATION — 1987-1992
Vice-President Medical Affairs

(a) Worked mainly with specialty product divisions, such as renal and cardiovascular, where end user influence is strong;

(b) Provided medical/scientific support regarding marketing, educational programs;

(c) Provided medical liaison and support to Baxter's Canadian regulatory group with respect to new product submissions, clinical trials; dealt directly with Health Protection Branch (Canada);

(d) Assisted in designing and monitoring several clinical trials in Canada;

(e) Responsible for external biotechnology assessment and transfer.

5. TORONTO WESTERN HOSPITAL 1965-1987

(i) Director, Division of Nephrology, 1972-1987

(a) Developed an internationally recognized academic nephrology division with a full range of clinical, teaching and research programs;

(b) Recruited five additional geographic full-time staff each of whom developed international reputations in clinical and/or basic research. Three of them are recognized as having made major therapeutic advances in haemodialysis, peritoneal dialysis, and renal transplantation;

(c) Created an environment in which everyone involved in the program, including allied services (nursing, laboratories, social services, etc.) functioned as a team whose goals were to provide optimal patient care in an atmosphere which fostered research and education;

(d) Developed an internationally recognized training program in Nephrology;

(e) Carried out all the usual functions of an academic physician including undergraduate and postgraduate teaching as well as serving on multiple departmental, hospital and university committees.

(ii) Director, Dialysis and Transplantation Program, 1965-1972

(a) Started Ontario's first formal dialysis and renal transplantation program which by 1987 had developed into one of Canada's 1,000 renal transplants performed;

(b) In connection with the program, initiated the following external support functions:

- The Ontario Branch of the Kidney Foundation of Canada
- The first transplant organ sharing network in Ontario
- The organ donor publicity program including having a consent form placed on the driver's license.

6. POST GRADUATE AND SPECIALTY TRAINING 1957-1965

1962-1965 Subspecialty Training in Nephrology - Methodist Hospital, Houston, Texas

1960-1962 Internal Medicine and Pathology - Royal Victoria Hospital, Montreal, Quebec

1958-1959 General Practice - Sudbury and Cambridge, Ontario

1957-1958 Internal Medicine - Shaughnessy DVA Hospital, Vancouver, B.C.

7. EDUCATION AND SPECIALTY QUALIFICATIONS

1956 M.D. - University of Toronto

1963 Fellow - Royal College of Physicians and Surgeons of Canada

1964 Diplomate - American Board of Internal Medicine

8. PROFESSIONAL APPOINTMENTS

1983-1985 President, Kidney Foundation of Canada (Ontario Branch)

1982-1983	President, Canadian Transplantation Society
1980-1984	Co-ordinator, Undergraduate Clinical Methods Teaching, Toronto Western Hospital, Toronto
1980-1984	Chairman, Medical Education Committee, Department of Medicine, Toronto Western Hospital, Toronto
1974-1975	President, Medical Staff Association, Toronto Western Hospital, Toronto
1972	Associate Professor, Department of Medicine, University of Toronto
1970-1974	Co-ordinator, Postgraduate Nephrology Training Program, University of Toronto

9. MEMBERSHIPS

1981	Member, Canadian Transplantation Society (Founding)
1977	Member, Canadian Society for Immunology
1975	Member, American Society of Transplant Surgeons & Physicians
1972	Member, International Society of Nephrology
1970	Member, American Society of Artificial and Internal Organs
1969	Member, International Transplantation Society
1967	Member, Canadian Society of Nephrology (Founding)
1966	Member, American Society of Nephrology

10. AWARDS

1991	Initial recipient of Kidney Foundation (Ontario Branch) Annual Distinguished Service Award (created in my name)

1990	David Ornstein National Distinguished Service Award Kidney Foundation of Canada
1966	Best Clinical Teacher, Department of Medicine Toronto Western Hospital

EXHIBIT B

BIBLIOGRAPHY-GEORGE A. DEVEBER

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2. Fluid and Electrolyte Problems in the Postoperative Period. Nursing Clinics of North America: 275-284 (1966)

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4. Effect of Haemodialysis on Thyroid Function. deVeber, G.A. and Schatz, D.L. Proc. European Dialysis & Transplant Ass. 226-229(1968)

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12. Excretion and Metabolism of Reserpine in Renal Failure. Zsoter, T.T., Johnson, G., deVeber, G.A. & Paul, H. Clinical Pharmacology & Therapeutics, Vol. 14, No. 3, pp. 325-330, May - June, (1973)

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